学校编码：10384　　分类号_____密级_____
学号：20620061152041　　UDC _____

厦门大学

硕 士 学 位 论 文

盐酸小檗碱生物可降解缓释体系的制备和性能研究

Preparation and characteration of biodegradable drug delivery systems encapsulating berberine hydrochloride

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论文提交日期：2009 年 6 月
论文答辩时间：2009 年 月
学位授予日期：2009 年 月

答辩委员会主席：_____
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2009 年 06 月

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摘　要

本文以生物可降解材料淀粉、海藻酸钠以及羧甲基壳聚糖为材料，分别制备了淀粉和海藻酸钠互穿网络型复合微球及海藻酸钠微球/羧甲基壳聚糖凝胶复合体系。采用改进的乳化凝胶法制备复合微球，用生物显微镜和扫描电镜考察了微球的形态，微球在水中形态圆整，分散性良好，干燥后在扫描电镜下仍然可以保持较好的形态，略有坍塌的现象。激光粒度分析仪考察了微球的粒径分布，微球的粒径分布受制备条件的影响，搅拌速度和油水比对粒径影响较大，增大搅拌速度和降低油水比可以使粒径变小，同时使粒径分布变均匀，油水比过低不利于乳液的形成，经过试验证实，油水比 2：1 有利于制备粒径均匀的微球。影响微球粒径的还包括聚合物浓度等。红外光谱证实海藻酸钠和淀粉良好地混合。本文以植物提取物盐酸小檗碱为模型药物，考察了药物在微球内的包封率及载药率，最高包封率可达 80%以上，用激光共聚焦显微镜考察了药物在微球内的分布状况，发现药物可以在微球内均匀分布。分别以 pH7.4 磷酸盐缓冲液和 pH1.2 盐酸溶液为释放介质，在 37±0.5°C 和 50r/min 的条件下考察了盐酸小檗碱在两种介质中的释放，用紫外分光光度计在 345nm 处测定药物浓度，发现盐酸小檗碱在磷酸盐缓冲液中释放较快，且有一定的突释效应。而在盐酸中缓释效果较好，通过拟合释放数据发现一级释放方程的拟合度最高。为了达到更好的缓释效果并减少突释效应，制备了海藻酸钠微球/羧甲基壳聚糖凝胶复合体系。金相显微镜和扫描电镜考察了复合体系的表面形态，可见微球分散于凝胶中，微球含量高的凝胶所观测到的微球数量较多。机械性能测试表明复合体系的抗压性能优于单纯凝胶，微球含量的增加会稍微降低抗压模量。考察了复合体系在 pH7.4 磷酸盐缓冲液(PBS)、pH1.2 盐酸溶液(HAS)和 pH6.3 生理盐水中释放，缓释效果相对于单纯微球大大改进。

关键词：海藻酸钠；微球；羧甲基壳聚糖；控制释放

Abstract

The present work used starch, alginate and carboxymethyl chitosan (CMC) to prepare starch/alginate interpenetrating polymer network (IPN) microspheres and alginate microsphere/ CMC hydrogel drug delivery system (DDS). Modified emulsification/gelation method was used to prepare blend microspheres. Microscopy and SEM were used to observe the morphology. The microspheres kept spherical and well dispersed in water. The microspheres can basically keep spherical with little deformation after freeze-drying which could be observed by SEM. The size distribution was mainly affected by preparation conditions especially stirring speed and O/W ratio. Increasing stirring speed and decreasing O/W ratio would cause a decrease in size and uniform size distribution. We found that 2:1 was a proper W/O ratio. Polymer concentration also affected size and size distribution. FTIR proved that the two polymers were well mixed. We took berberine hydrochloride as a model drug to be encapsulated by the blend microspheres. Highest encapsulation efficiency of more than 80% was achieved by using proper conditions. Confocal laser scanning microscopy(CLSM) was used to observe the drug distribution in microspheres. Drug distribution was uniform. Drug release performance was studied in both pH 7.4 phosphate buffer solution(PBS) and pH 1.2 hydrochloride acid solution (HAS)at 37±0.5° C and 50 r/mmin.The drug concentration was determined by UV at 345 nm. It was found that release in PBS was fast and a considerable burst release happened. On the contrary, a delayed release was noted in HAS. The release data were fitted with several classic models. It was found that a first-order model fitted best. In order to get more delayed release and decrease burst release, new DDS of alginate microsphere/CMC hydrogel was prepared. The surface morphology was observes with metallographic microscope and SEM. Microspheres could be seen to be distributed in hydrogel. More microspheres could be seen in DDS with more microspheres added. Mechanical test proved that DDS had better compressive strength than pure hydrogel. But increase of microspheres would cause a little decrease of compressive strength. Release performance was studied in pH1.2 HAS、pH7.4 PBS and pH6.3 saline solution. More delayed release was found compared to pure microspheres.

Keywords: Alginate; Microspheres; Carboxymethyl chitosan; Controlled release

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